Universitat Autònoma de Barcelona

# THERAPY – RELATED LEUKEMIA
## TOPOISOMERASE II INHIBITORS: FRIEND OR FOE?

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## Introduction

❑ **Therapy – related leukemia** (t-MN) is far from being a well known syndrome, but progress is being made. It is a distinctive clinical syndrome in patients with preceding solid tumor or hematologic malignancies that were treated with **cytotoxic procedures** . Because there is an increasing number of cured patients at risk of developing Therapy – Acute Myeloid Leukemia due to prior radio or chemotherapies, bigger efforts are made in order to gain further knowledge.

❑ There is close association between distinct subtypes of t-MN and the nature of previous treatment:

| | |
|---|---|
| Alkylating agents | • MDS with chr. 7 and/or 5 loss/rearrangement/deletion<br>• Latency from 3-7 years after cytotoxic exposure |
| Topoisomerase II inhibitors | • Balanced translocations involving *MLL, AML1,* ...<br>• Younger age, directly AML and shorter latency after exposure |

❑ It gives us a unique chance to assess the effects of carcinogenesis and mutagens in humans, and to analyse individual predisposing factors.

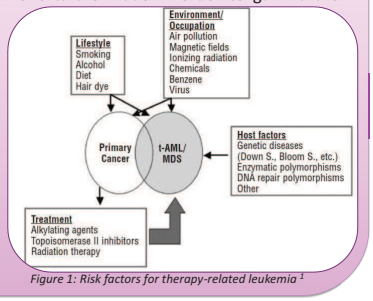



*Figure 1: Risk factors for therapy-related leukemia* [1]

## Methodology

As a **literature review**, information was extracted from several articles on scientific databases, searching for the following key-words: secondary malignancies, therapy-related leukemia, topoisomerase II inhibitors. Other material was consulted in order to solve concept misunderstandings. For the written report, the most relevant information was selected.

## Objectives

The aim of this work is to understand what are therapy-related leukemias, specially the role that **topoisomerase II inhibitors** have on them. In this line, find information about what these agents **cause** and if there are any **alternative treatments** in order to avoid their use.

## Topoisomerase II inhibitors

**Topoisomerase II** is a critical enzyme that relaxes supercoiled DNA by transiently cleaving and religating both strands of the double helix through the formation of a covalent cleavage intermediate

Biological function: crucial for insuring genomic integrity → Capability to interfere with it (enzyme mediated DNA damage) → Effective strategy for cancer chemotherapy ⇩ **Topoisomerase II inhibitors**

**Topoisomerase II inhibitors**
- Topoisomerase II poisons → Most of the clinically active agents
- Topoisomerase II catalytic inhibitors → Drug's nature related to molecular phenotype of t-MN

❑ **Mechanism of action**: Block the enzymatic reaction through religation and enzyme release, leaving DNA with a permanent strand break (=apoptosis).
→ Leukemogenic and antineoplastic effect → chromosomal breakages resolved by chromosomal translocation (leukemic transformation)

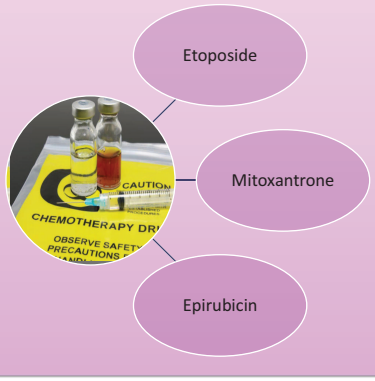
❑ **Side effects:** Onset of a wide spectrum of secondary malignancies due to topoisomerase II inhibitors administration (high potential to generate translocations)

❑ **Clinical profile**
- Rarely preceded by t-MDS
- Shorter latency (2-3y from 1st exposure)
- Rapidly progressive leukemia

❑ **Individual susceptibility factors:**
→ Genetic polymorphisms in

| Drug metabolizing enzymes | DNA repair processes |
|---|---|
| GST genes with variant alleles related with a decrease in enzymatic activity | ↓ rates of repair |
| ↓ | ↓ |
| ✓Higher DNA damage<br>✓Greater toxicity<br>✓Reduced survival | Inhibition of apoptosis, committed cell survives |
| | ↑ rates of repair |
| | ↓ |
| | persistence of mutations |

### Some examples



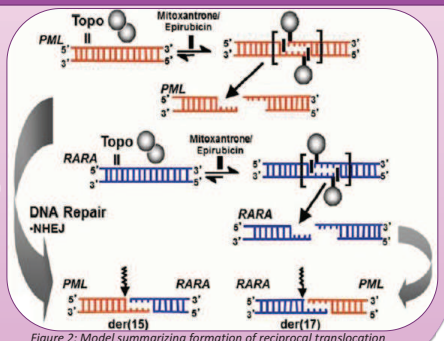




*Figure 2: Model summarizing formation of reciprocal translocation breakpoint junctions after treatment of mitoxantrone and epirubicin in t-APL* [2]

## New treatments

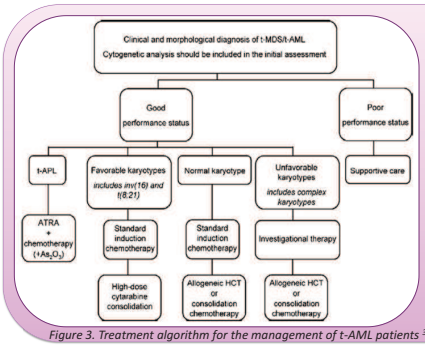



*Figure 3. Treatment algorithm for the management of t-AML patients* [3]

❑ Poor hematopoietic reserves make the administration of standard AML therapy difficult because of:
- **Low tolerance** for the high toxicity of treatments used
- Multidrug **resistance** phenotype (t-MN emerges during the treatment of previous chemotherapy)

| | |
|---|---|
| Previous screening | • Strongest predictors for severity/overall survival ➡ cytogenetic abnormalities<br>• Treatment algorithm for patients performance status (*fig 3.*) |
| New therapies with AAV vectors | • Gene therapy is becoming a new reality in different treatments<br>• Some interesting results with AAV8-IL24 in *MLL/AF4* - Acute Limfoblastic Leukemia cells<br>• IL24 induces apoptosis, immunomodulatory and antiangiogenic effects in cancer cells |
| Alternative drugs | • Daurinol: Catalytic inhibitor of hTopoisomerase IIa, similar to etoposide but without severe DNA damage |

## Discussion

Effective anticancer treatments ➡ increase in survival/overall cure rate ➡ ↑ more cases of people with secondary leukemia due to previous treatments

❑ **Shortage of data** from treatments to previous malignancies, together with few data from t-MN patients ➡ needed to expand current knowledge
❑ **Prevention** using less leukemogenic compounds when possibly, while implementing schedules with longer period and lower dosage
❑ **Individual susceptibility** from differences in membrane transport, drug catabolism an inefficient DNA repair ➡ study of polymorphisms involved
❑ **Emergence of new treatments** could lead to a progressive disappearance of leukemogenic agents in protocols ➡ gene therapy is a promising tool
❑ Important to **aware clinicians** about the pros and cons of using topoisomerase II inhibitors

**It is of high priority to gain further knowledge of topoisomerase II inhibitors and their role on therapy – related leukemia**

## Bibliography

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3. Godley LA, Larson RA (2008). Therapy-related myeloid leukemia. *Seminars in Oncology*, *35*(4), 418–429